ABC of smoking cessation

Bupropion and other non-nicotine pharmacotherapies

Elin Roddy

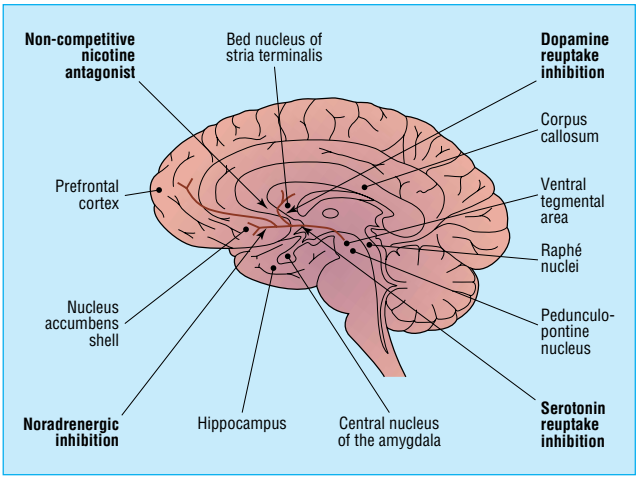
Although nicotine replacement has been the first line drug treatment for smoking cessation for many years, other drugs of proved efficacy are also now available. Foremost among these is bupropion (marketed as Zyban). Bupropion was developed and initially introduced in the United States as an antidepressant but was subsequently noted to reduce the desire to smoke cigarettes and shown in clinical trials to be effective in smoking cessation.

Bupropion is the only non-nicotine drug licensed for use in smoking cessation in the United Kingdom and the European Union; it became available for use in 2000

Mechanism of action

Bupropion is an atypical antidepressant structurally similar to diethylpropion, an appetite suppressant. The mechanism of the antidepressant effect of bupropion is not fully understood, but bupropion inhibits reuptake of dopamine, noradrenaline, and serotonin in the central nervous system, is a non-competitive nicotine receptor antagonist, and at high concentrations inhibits the firing of noradrenergic neurons in the locus caeruleus.

It is not clear which of these effects accounts for the antismoking activity of the drug, but inhibition of the reductions in levels of dopamine and noradrenaline levels in the central nervous system that occur in nicotine withdrawal is likely to be important. The antismoking effect of bupropion does not seem to be related to the antidepressant effect as bupropion is equally effective as a smoking cessation therapy in smokers with and without depression.



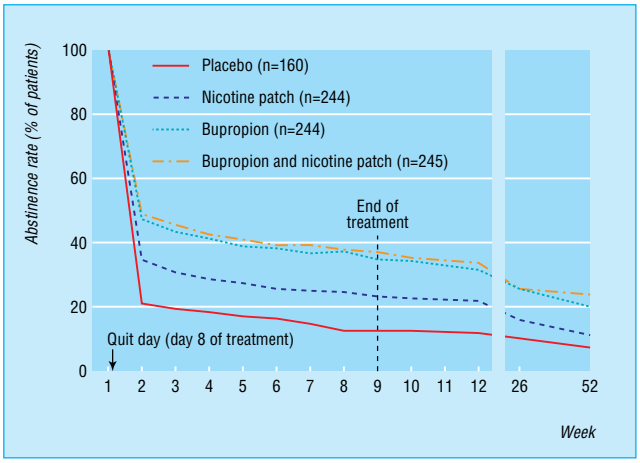
Effects of bupropion on the central nervous system

Evidence for effectiveness

When given in association with intensive behavioural support, bupropion is as effective as nicotine replacement therapy (NRT), and like NRT, leads to a near doubling of the smoking cessation rate, achieving long term abstinence in 19% of smokers who use it to quit.

The effectiveness of bupropion in conjunction with less intensive levels of behavioural support has not been tested in clinical trials. Like NRT, however, bupropion therapy probably increases the chance of success with any quit attempt but is most effective when combined with intensive behavioural support. No evidence suggests that bupropion is any more or less effective in any specific subgroups of smokers, such as those in hospital or those with a smoking related disease.

Bupropion also seems to attenuate the weight gain that often occurs after quitting. More prolonged use of bupropion (beyond the recommended eight weeks) seems to confer further protection against relapse.

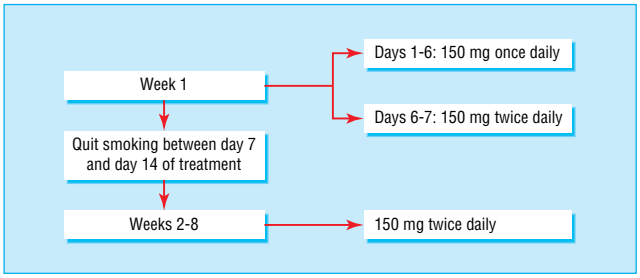


Abstinence from smoking in relation to sustained release bupropion or nicotine patch, or both. Adapted from Jorenby et al. *N Engl J Med* 1999;340:685-91

Using bupropion

Dose

Bupropion is marketed in the United Kingdom as an oral prolonged release 150 mg tablet. An eight week course of treatment is recommended and costs about £86 ($143; €123). Smokers should start taking bupropion one week before their intended quit date. A reduced dose—that is, one tablet daily—is recommended in elderly people and those with liver or renal impairment.



Dose regimen for bupropion

Unwanted effects

The most serious adverse effect of bupropion is seizure, which affects an estimated 1 in 1000 users. More common side effects include dry mouth, insomnia, skin rash, pruritus, and hypersensitivity. Rarely the drug may cause a reaction resembling serum sickness.

Contraindications and precautions

Bupropion is contraindicated in patients with current or past epilepsy. It should also be used with extreme caution in patients with conditions predisposing to a low threshold for seizure —history of head trauma, alcohol misuse, diabetes treated with hypoglycaemic agents or insulin—and in patients taking drugs that lower the seizure threshold (for example, theophylline, antipsychotics, antidepressants, and systemic corticosteroids).

Bupropion is also contraindicated in patients with a history of anorexia nervosa and bulimia, severe hepatic necrosis, or bipolar disorder.

Power of the press

- The use of bupropion has been inhibited in the United Kingdom by a series of articles in national newspapers soon after the drug was launched
- These implicated bupropion in some serious adverse effects, including death, in a number of cases
- Post-marketing surveillance has since shown that serious adverse events are rare with bupropion, occurring at about half the average reported rate for new drugs in Britain

Bupropion should not be used with a monoamine oxidase inhibitor, and at least 14 days should elapse between stopping such treatment and starting bupropion

Pharmacokinetics and interactions

Bupropion reaches a peak plasma concentration three hours after oral administration, with steady state concentration reached within eight days. It has a half life of 20 hours and is metabolised in the liver by cytochrome p450.

Bupropion interacts with a number of commonly used drugs, including some antidepressants, type 1c antiarrhythmics, and antipsychotics

Interactions of bupropion

Drug	Mechanism of interaction	Action required
Antidepressants (desipramine, fluoxetine)	Prolongs action of drugs metabolised by cytochrome p450 (CTP2D6)	Start these drugs at low end of dose range in patients already taking bupropion. Decrease dose of ongoing treatment with these drugs if patient starts bupropion
Antipsychotics (risperidone, thioridazine)		
Type 1c antiarrhythmics (propafenone, flecainide)		
β blockers (metoprolol)		
Antiepileptics (carbamazepine, phenobarbitone, phenytoin)	Metabolism of bupropion induced	Bupropion dose increase not recommended*
Levodopa	Limited clinical data suggest higher incidence of adverse events	Give bupropion with caution to patients receiving levodopa
MAOIs (including moclobemide)	Avoid using bupropion for two weeks after MAOIs	
Ritonavir	Increased plasma bupropion concentration; risk of increased toxicity	Avoid concomitant use

MAOI = mono amine oxidase inhibitor.
*Bupropion contraindicated in epilepsy.

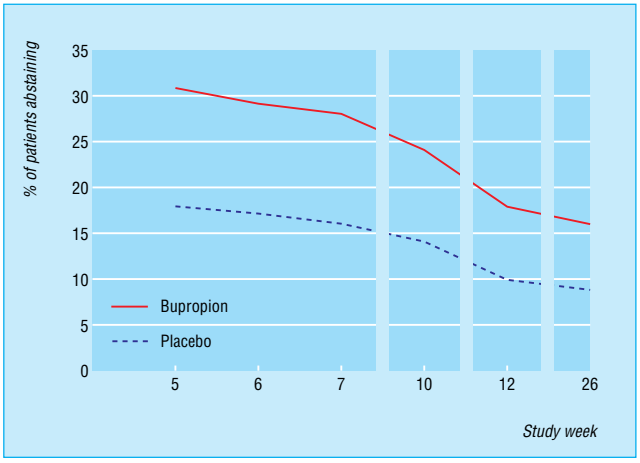
Use with NRT

One study has suggested that combined nicotine patch therapy and bupropion may produce higher quit rates than nicotine patches alone. Combination therapy may therefore be recommended to patients attending specialist cessation clinics who find it difficult to quit using a single pharmacotherapy. Monitoring for hypertension is recommended when combined therapy is used.

Special groups

Chronic obstructive pulmonary disease—Smoking cessation is the most important intervention in this disease. Bupropion has been shown to be effective and well tolerated in this group of patients.

Ischaemic heart disease—Smoking cessation is one of the most important interventions in this disease. Bupropion is not contraindicated or subject to caution except in diabetic patients treated with hypoglycaemic agents or insulin (caution) or in patients taking propafenone or flecainide (dose reduction of antiarrhythmics advised).



Long term abstinence from smoking in patients with chronic obstructive pulmonary disease, after treatment with bupropion. Adapted from Tashkin et al. *Lancet* 2001;357:1571-5

Pregnant women—No trials of bupropion have been done in pregnant women. Bupropion is therefore not recommended for use in pregnancy.

Other antidepressants

Nortriptyline, a tricyclic antidepressant with mostly noradrenergic properties and a small amount of dopaminergic activity, is also effective in cessation therapy, and although few clinical trials have been done, these suggest an effect of similar magnitude to that of bupropion. Again, this effect seems to be independent of the presence of depressive symptoms.

Several other antidepressants have been used in smoking cessation including imipramine, doxepin, venlafaxine, fluoxetine, and the reversible monoamine oxidase inhibitor moclobemide. The latter may be effective in some patients, but the effectiveness of other therapies is unproved.

Other pharmacotherapies

Clonidine is an α noradrenergic agonist that suppresses sympathetic activity and has been used for hypertension and to reduce withdrawal symptoms associated with misuse of alcohol and opiates. Both in its oral and low dose patch formulation, clonidine increased smoking cessation in eight out of nine trials, but the drug is associated with serious side effects, including sedation and postural hypotension. Clonidine is therefore probably best reserved for smokers who cannot or do not wish to use NRT, bupropion, or nortriptyline.

Mecamylamine is a nicotinic antagonist originally used to decrease cholinergic activity and thus reduce blood pressure. It blocks the effects of nicotine but does not precipitate withdrawal symptoms. Two trials have suggested that a low dose mecamylamine patch combined with a nicotine patch was superior to placebo, but a recent multicentre trial has failed to show efficacy.

Sensory replacement therapy could be useful for the many smokers who report missing the sensory aspects of smoking. Sensory effects of smoking are important in reinforcing smoking behaviour, and loss of these effects may contribute to relapse. Two inhalers containing ascorbic acid or citric acid have been tested, and both increased rates of short term cessation. Further testing of these adjuncts to NRT or other non-nicotine therapies is warranted, but neither of these treatments is currently used routinely in specialist cessation clinics.

Competing interests: ER has been reimbursed by GlaxoSmithKline, the manufacturer of bupropion, for attending one international meeting and has attended educational events sponsored by Pharmacia, the manufacturer of Nicorette. See first article in this series (24 January 2004) for the series editor's competing interests.

No trials of bupropion have been done in smokers aged under 18, and the drug is not licensed or recommended for smoking cessation in this age group

Non-nicotine therapies for smoking cessation

Proved effective—Bupropion, clonidine, nortriptyline
Possibly effective—Noradrenergic antidepressants, monoamine oxidase inhibitors, mecamylamine plus nicotine replacement therapy, sensory replacement
Ineffective or insufficient evidence—Anorectics, benzodiazepines, β blockers, buspirone, caffeine, ephedrine, cimetidine, dextrose, lobeline, naltrexone, ondansetron, phenylpropanolamine, silver acetate, stimulants, selective serotonin reuptake inhibitors

Key points

- NRT is the treatment of choice, but non-nicotine drugs are also available as an alternative
- Bupropion is the most commonly used non-nicotine treatment
- Bupropion is generally safe and well tolerated
- Bupropion is as effective as NRT and doubles quit rates when given alongside intensive behavioural support
- Bupropion must not be given to patients at increased risk of seizures
- Nortriptyline has been less widely studied, but its effectiveness seems similar to that of bupropion
- Any risks associated with these therapies are likely to be much less serious than the risks from continued smoking

Further reading

- Antidepressants for smoking cessation. *Cochrane Database Syst Rev* 2003;(3):CD000031
- Royal College of Physicians of London. *Nicotine addiction in Britain.* London: RCP, 2000.
- Hurt RD, Sachs DPL, Glover ED, Offord KP, Johnston JA, Dale LC, et al. A comparison of sustained-release bupropion and placebo for smoking cessation. *N Engl J Med* 1997;337:1195-202.

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The ABC of smoking cessation is edited by John Britton, professor of epidemiology at the University of Nottingham in the division of epidemiology and public health at City Hospital, Nottingham. The series will be published as a book in the late spring.

BMJ 2004;328:509–11

General practice 2035

My driver pulled up outside the house. Wearily, I eased myself out of the car, wincing from the pain of my osteoarthritic spine. The patient's husband met me at the door and mumbled something. I turned up my hearing aids and asked him to repeat what he had said.

"I didn't like the attitude of the doctor I spoke to over the phone," he shouted. "My wife couldn't possibly get down to the call centre in her state."

I climbed the stairs. Gasping for breath at the top, I went into the bedroom and found that my respiration rate matched that of the patient. She was in left ventricular failure. I injected her with furosemide. At least, I think it was furosemide. The print on the ampoules is so small these days.

As I came downstairs, my right knee gave way, and I fell in a crumpled heap at the bottom. Putting my false teeth back in and straightening my wig, I slowly got to my feet. The husband asked whether I wasn't too old to be a doctor. I pulled myself up to my full osteoporotic height and, peering through my cataracts, told him in no uncertain terms that nowadays he was lucky to get a doctor at all. And with that I stomped off into the night as fast as my gout would allow me.

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